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Neural Circuits and Mechanisms of Post-Traumatic Stress Disorder

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A functional neuroanatomy that can account for the spectrum of symptoms associated with Post-Traumatic Stress Disorder (PTSD) has not been definitively established. The long-held idea that limbic brain structures and their projections constitute a functional system mediating emotional behavior has been questioned (1). However, there is neuroanatomical, neurophysiological, and neurochemical evidence supporting the concept of a neural circuit consisting of brain structures within and outside the limbic forebrain that can mediate the effects of traumatic stress (2).

The brain structures constituting such a neural circuit should have several features. There needs to be sufficient afferent sensory input to permit assessment of the fear- or anxiety-producing nature of the traumatic event. The neuronal interactions among the brain structures must be capable of incorporating an individual's prior experience (memory) into the cognitive appraisal of the event. These interactions are important in the attachment of affective significance to specific stimuli and the mobilization of adaptive behavioral responses. Finally, the efferent projections from the brain structures should be able to mediate an individual's neuroendocrine, autonomic, and skeletal motor responses to original traumas, as well as account for the pathological reactions to subsequent traumatic reminders that result in anxiety-related signs and symptoms.

Preclinical and clinical investigations provide strong evidence for linking several brain structures to the signs and symptoms of anxiety and fear associated with trauma. Chief among these are the amygdala, locus coeruleus, hippocampus, hypothalamus, thalamus, periaqueductal gray, and orbitofrontal cortex. In the sections to follow, the neuroanatomy, neurochemistry, and neural mechanisms relevant to the role these brain structures play in anxiety and fear are reviewed. The implications of these findings for a better understanding of the pathophysiology and treatment of PTSD are also discussed.

KEY BRAIN STRUCTURES MEDIATING ANXIETY AND FEAR BEHAVIORS RESULTING FROM TRAUMATIC STRESS: THE AMYGDALA

Neuroanatomy

Afferent Pathways

The amygdala receives an extraordinary afferent input that forms the basis for the pivotal role of the amygdala in the processing of fear- and anxiety-inducing stimuli, as well as the organization of adaptive behavioral, autonomic, neuroendocrine, and skeletal-motor responses.

Brain stem afferent pathways to the amygdala include those from the parabrachial nucleus (3,4) and locus coeruleus (5,6). Among the subcortical afferent pathways to the amygdala are those from the posterior thalamus and the entorhinal cortex (7,8). The amygdala also receives an extensive innervation from visual, auditory, and somatosensory systems in the cortex (9).

Efferent Pathways

The central nucleus of the amygdala, but not other amygdala nuclei, descend into and through the midbrain, pons, and medulla. These projections innervate a number of brain structures implicated in autonomic control, including the dorsal motor nucleus of the vagus (10) and parabrachial nucleus (3,4), which may mediate fear-induced autonomic and respiratory changes, respectively.

The central and basal amygdaloid nuclei amygdala return the substantial noradrenergic input from the locus coeruleus (LC) (5,6). There are also indirect projections to the LC via the paragigantocellularis nucleus (11) and the ventral tegmental area (6). These projections may form the basis of important functional interactions between the LC and the amygdala, which are discussed in detail in the paragraphs that follow.

The subcortical connections of the amygdala include the amygdala-striatal projections, which are among the most substantial efferents of the amygdala. The region of the striatum that receives amygdaloid projections also receives efferents from the prefrontal cortex and dopamine neurons in the ventral tegmentum, and has been termed the "limbic striatum" (12). These interactions may be critical in developing motor responses to threatening environmental stimuli, especially in utilizing past experience (13,14).

There are direct projections from the central nucleus of the amygdala to the lateral hypothalamus (15,16). These projections may be involved in the activation of the sympathetic autonomic nervous system produced by traumatic stress (4). Direct projections from the central nucleus of the amygdala to the paraventricular nucleus of the hypothalamus (17–19), or indirect projections by way of the bed nucleus of the stria terminalis and preoptic area, which receive inputs from the amygdala (7) and project to the paraventricular nucleus (20), may mediate the neuroendocrine responses to stressful or fearful stimuli (19).

There are important anatomical interconnections between the hippocampus and the amygdala (21,22). The amygdala projection to the hippocampus is substantially stronger than hippocampal projections to the amygdala. The predominant amygdala projections to the hippocampus are from the lateral nucleus, magnocellular division of the accessory basal nucleus, and the parvicellular division of the basal nucleus.

The amygdala has an extensive reciprocal innervation with the cortex (23). The amygdala projects to essentially all visually related areas of temporal and occipital cortex. There are also substantial connections between the amygdala and polysensory regions of temporal, insular, cingulate, and frontal lobes (24). In addition to via the extensive, direct interconnections between the amygdala and prefrontal cortex, the amygdala can influence the prefrontal cortex through the thalamus and striatum (13,14).

Behavioral Effects of Stimulation of the Amygdala

In laboratory animals, electrical stimulation of the amygdala produces a complex pattern of behavior consistent with the animal being frightened (25–27). Amygdala kindling increases fear responses without altering spatial memory (28). In addition, stimulation of the amygdala results in changes in autonomic, neuroendocrine, and reflex function that frequently accompany fear and anxiety states. Numerous investigations have demonstrated that respiration, blood pressure, and heart rate are increased by amygdala stimulation (see review [4]). There is also an elicitation of jaw movements (25,26, 29) and activation of facial motor neurons (30), which probably relates to the involvement of the amygdala in facial recognition (31) and the

alteration in facial expression that occurs with fear. Numerous brain reflexes are generally enhanced by amygdala stimulation, including the massenteric (32), baroreceptor (33), nictitating membrane, (34) and startle reflexes (4). Finally, electrical stimulation of the amygdala increases plasma levels of corticosterone (35,36) (see review [4]).

Electrical stimulation of the amygdala in humans has been investigated in patients with temporal lobe epilepsy (37–39). A variety of emotions are elicited by amygdala stimulation, including fear, anxiety, pleasure, and anger, with fear reported most frequently. It is noteworthy that the emotional content associated with the affect produced by amygdala stimulation has often been related to both the individual's current psychological concerns and past experience. In this context, many of the experiental phenomena produced have had the quality of flashbacks. These clinical investigations suggest that a primary function of the amygdala may be to bring perceptions and memories stored in other brain structures (cortex) to a conscious level, thereby linking an individual's encoded personal life experience with a current life event, resulting in an individualized motivational and affective state (37). This hypothesis is supported by the extensive reciprocal innervation of the neocortex and amygdala. These neuronal interactions may form the basis of the persistent, intrusive memories associated with PTSD and the distressing effects of reminders of the original trauma.

BEHAVIORAL EFFECTS OF AMYGDALA LESIONS

Lesions of the amygdala in laboratory animals result in a spectrum of changes in behaviors, including reduced aggression, a generalized reduction in emotional responsiveness, increased orality, and altered responses to food (40). Numerous investigators have suggested, based upon lesion studies and the neuroanatomy of the amygdala, that the amygdala is critical to the learning of stimulis-reinforcement associations (41,42). In studies of the effects of amygdala lesions on social behavior in monkeys, a consistent observation in lesioned animals is the loss of the ability to attach meaning to sensory information in order to generate appropriate behavioral responses (43,44). In several different species, lesions of the amygdala have been shown to reduce fear (4). Amygdala lesions will greatly increase the number of contacts a rat will make with a sedated cat (45), and reduce the effect of restraint stress on gastrointestinal ulceration and hypersecretion of corticosterone (46–48).

Studies of lesions of the amygdala suggest an important role for the amygdala in the mechanisms underlying fear conditioning. Lesions attenuate conditioned freezing normally seen in response to a stimulis formerly paired with a shock (45,49,50) or a dominant male rat (51,52). Amygdala lesions antagonize the reduction in bar pressing in the operant conflict test (53) and the fear potentiated startle (54).

Direct Recording of Amygdala Activity During Different Behavioral States

The hypothesis that the amygdala contributes to the assessment of the emotional significance of sensory stimuli is further supported by the results of investigations recording amygdala neural activity (55). While amygdala neurons are responsive to single sensory stimuli (flashing lights, clicks), they are more sensitive to complex sensory events with emotional significance, and rewarding and aversive stimulis properties (55–58). For example, a group of neurons in the amygdala are involved in facial recognition and the resultant emotional and social responses (59–60). These neurons receive input from cortical neurons in the temporal lobes (61) that provide information regarding facial identity and expression (62), which will then predispose the organism toward a specific behavioral response.

Several studies have examined amygdala activity in relation to presentation of conditioned stimuli. It has been demonstrated that a neutral stimulis paired with aversive stimulation will increase neural firing in the amygdala (63–65). In the nonhuman primate, amygdala activity is increased with stimuli of high emotional significance, especially threat. This is true both for

auditory and visual stimuli (66). There is preliminary data in humans that amygdala neural activity is increased during highly charged emotional states (67). These data, from amygdala lesion and recording studies, point not only toward a critical role for the amygdala in initial assessment and behavioral response to traumatic events to longer term consequences of trauma.

THE LOCUS COERULEUS

Neuroanatomy of the Locus Coeruleus

Afferent Pathways

The neuroanatomy of the largest central noradrenergic nucleus, the locus coeruleus (LC), is characterized by an extensive efferent projection system and a more restricted afferent input (68–70). A retrograde labeling study of afferent input to the LC using iontophoretic horseradish peroxidase (HRP) injections found that forebrain structures such as the neocortex, amygdala, and hypothalamus project to the LC. The hypothalamic innervation is noteworthy because it provides a potential regulatory role for the LC on autonomic function. Brain stem monoaminergic neurons, such as the raphe nuclei and a variety of sensory relay areas, also project to the LC. The existence of these sensory afferents from the spinal cord and nucleus of the solitary tract provide insight into the mechanisms by which the LC is responsive to noxious stimuli and alterations in cardiovascular function (71). Consistent with these observations, a recent neuroanatomical investigation involving anterograde labeling with PhA-L in the cat and monkey found terminal fibers in the LC following injections in lamina 1 of the spinal or medullary dorsal horn (69). These observations are supported by an electrophysiological mapping study revealing that spinal cord lamina 1 cells terminated in the locus coeruleus (70). Contradicting these observations are reports that direct afferents to the LC almost exclusively come from the paragigantocellularis (PG) and the prepositus hypoglossi (PrH) (72). These studies used very small injections of wheat germ agglutinin conjugated to HRP (WGA-HRP) that were restricted to the LC in the rat. The discrepant observations may be due to the fact that WGA-HRP is not an efficient retrograde marker for lamina 1 neurons (73). The finding of additional afferents to the LC using choleratoxin B subunit as a retrograde tracer instead of WGA-HRP is consistent with this assertion (74). The hypothesis that PGi and PrH are the predominant afferents to the LC is also not supported by the demonstration that destruction of these nuclei fail to block LC responses to somatosensory stimuli (75).

If not the primary LC afferent, the PGI remains an important afferent to the LC and is a key sympathoexcitatory region in brain (68). There are widespread afferents to the PGI from diverse brain areas (76). The PGI may be an integrative pathway for activating the LC by a variety of mechanisms. The PGI is involved in control of arterial blood pressure, cardiopulmonary reflexes, and parasympathetic function. It has been suggested that the peripheral sympathetic nervous system is activated in parallel with the LC by projections to both areas from the PGI (68). The locus coeruleus also appears to be activated by projections responsive to corticotropin-releasing factor (CRF), and considerable evidence suggests that CRF has anxiogenic properties. Intracerebroventricular infusion of CRF increases norepinephrine turnover in several forebrain areas (77). The CRF in a dose-dependent fashion increases the firing rate of LC-norepinephrine neurons (78). Stress, which activates norepinephrine neurons, markedly increases CRF concentrations in the LC (79). Moreover, it has recently been demonstrated that infusion of CRF into the LC produces anxiogenic activity, as well as significant increases in the norepinephrine metabolite 3,4-dihydroxy phenylglycol in forebrain areas such as the amygdala and hypothalamus (80).

Efferent Pathways

The LC has diffuse projections to the entire cortical mantle, as well as thalamus, hypothalamus, amygdala, hippocampus, cerebellum, and spinal cord. Through this broad efferent network

the LC can mediate a range of cognitive, neuroendocrine, cardiovascular, and skeletal motor responses that accompany anxiety and fear.

The LC is the primary source of norepinephrine fibers in a number of neocortical regions in the primate. Consistent with postsynaptic inhibitory effects of norepinephrine, activation of the LC neurons produces inhibition of neuronal activity in brain regions receiving projections from the LC, including the cochlear nucleus, cerebral and cerebellar cortices, spinal trigeminal nucleus, hippocampus, caudate, and superior colliculus. Similarly, LC stimulation reduces cerebral metabolism and blood flow in these areas (81,82). Since norepinephrine has greater inhibitory effects on spontaneous than on evoked neuronal activity, it has been suggested that a function of the LC-norepinephrine system is to enhance neuronal responses to inputs of behavioral significance or, put another way, to increase the signal-to-noise ratio (10).

Behavioral Effects of Locus Coeruleus Stimulation

Electrical stimulation of the LC produces a series of behavioral responses similar to those observed in naturally occurring or experimentally-induced fear (83). These behaviors are also elicited by administration of drugs such as yohimbine and piperoxone that activate the LC by blocking alpha-2 adrenergic autoreceptors (84). Drugs that decrease the function of the LC by interacting with inhibitory opiate (morphine), benzodiazepine (diazepam), and alpha-2 (clonidine) receptors on the LC decrease fearful behavior and partially antagonize the effects of electrical stimulation of the LC in the monkey (85). These studies suggest that abnormally high levels of LC activity producing increased release of NE at postsynaptic projection sites throughout the brain may act to augment some forms of fear or pathological anxiety, depending on the environmental conditions.

Studies conducted in healthy human subjects and psychiatric patients are largely consistent with this assertion. Piperoxone and yohimbine cause anxiety in humans. Patients with panic disorder and post-traumatic stress disorder have abnormally increased responses to yohimbine (86–88). A single report of electrical stimulation of the LC region in humans reported that the subjects experienced feelings of fear and imminent death (89). In a subject with chronically implanted stimulation electrodes in the vicinity of the LC, electrical stimulation during sleep was associated with marked insomnia (90).

Behavioral Effects of Locus Coeruleus Lesions

Bilateral lesions of the LC in the monkey decrease the natural occurrence of fearful behavioral responses in a social group situation, and in response to threatening confrontations with humans (83). Agents that decrease the function of the LC also decrease fearful behavior and partially antagonize the effects of electrical stimulation of the LC in the monkey. Lesions of the dorsal bundle that originates in the locus coeruleus and projects mostly to the neocortex, hippocampus, and cerebellar cortex produce anxiolytic type responses in anxiogenic behavioral test situations (91).

Many studies in rodents using the neurotoxin, 6-OHDA, have shown effects on a variety of behavioral tests that have been interpreted as inconsistent with the hypothesis that noradrenergic systems are critically involved in anxiety and fear (92). The validity of these behavioral paradigms to reflect anxiety and fear has been the subject of much debate (83,84,93).

LOCUS COERULEUS ACTIVITY AND BEHAVIORAL STATES ASSOCIATED WITH STRESS AND FEAR

The effect of stressful stimuli on LC activity has been assessed in freely moving cats (94–97). Conditions that are behaviorally activating but not stressful, such as exposure to inaccessible rats or food, do not increase LC firing. In contrast, stressful and fear-inducing stimuli, such as loud white noise, air puff, restraint, and confrontation with a dog, produce a rapid, robust, and sustained increase in LC activity (94–97). Of

interest, these increases in LC function are accompanied by sympathetic activation. Generally, the greater the sympathetic activation in response to the stressor, as indicated by heart rate, the greater the correlation observed. Thus, a stimulus intensity threshold for coactivation of central and peripheral NE systems may exist.

A parallel activation of LC neurons and splanchnic sympathetic nerves is produced by noxious stimuli. The LC, like sympathetic, splanchnic activity, is highly responsive to various peripheral cardiovascular events such as alterations in blood volume or blood pressure. Internal events that must be responded to for survival, such as thermoregulatory disturbance, hypoglycemia, blood loss, an increase in pCO2, or a marked reduction in blood pressure, cause robust and long-lasting increases in LC activity (98–101).

There are also peripheral visceral influences on LC activity. In rats, distention of the urinary bladder, distal colon, or rectum activate LC neurons. These findings suggest that traumatic stress-induced changes in autonomic or visceral function may result in specific behavioral responses via the brain LC-norepinephrine system. The LC-norepinephrine network may be an important component of the efferent arm of circuits activated by traumatic stress. On the one hand, the system, when functioning normally, may be critical in facilitating the planning and execution of behaviors important for survival (98). On the other hand, it is possible that severe stress renders the system hyperresponsive subsequent to the stress, resulting in chronic anxiety-related symptoms.

OTHER BRAIN STRUCTURES IN THE NEURAL CIRCUIT OF FEAR

Thalamus

The thalamus is another brain structure important in fear responses. There is evidence from classically conditioned emotional responses that the processing of threatening stimuli involves the relay of sensory signals to limbic forebrain directly from the thalamus and cortex (102,103). Fear responses to acoustic stimuli are disrupted by thalamic lesions, and responses depend on the connection between the thalamus and amygdala (104).

Most importantly, as will soon be described in detail, the thalamus serves as an important link between peripheral sensory inputs and other brain structures that mediate fear responses. The thalamic nuclei relay sensory information from auditory, visual, and somesthetic systems to the cortex and limbic forebrain. Thus, the thalamus is an important neuronal interface between the environment and forebrain structures.

Hippocampus

The hippocampus has been hypothesized to play a key role in anxiety development. Lesions of the hippocampus increase punished responses like anxiolytic drugs (105). Hippocampal lesions have little effects on classically conditioned, modality-specific fear, in contrast to the amygdala (106). Furthermore, there is recent data that damage to the hippocampus formation in monkeys impairs memory, but does not affect emotional behavior. In contrast, damage to the amygdaloid complex alters emotional behavior, but not memory (107,108).

However, there is evidence of a sensory relay role for the hippocampus in fear conditioning. Lesions of the hippocampus interfere with conditioning of fear responses to polymodal contextual stimuli (106,109). It has been speculated that the role of the hippocampus in contextual fear conditioning involves projections from the subiculum to the amygdala (106).

There is strong evidence that the cortical projections relaying sensory information to the hippocampus play a role in many cognitive functions (108,110–112). Projections from the amygdala to the hippocampus could permit the experience of fear to modulate or influence shortterm memory function. The neuronal loop among the cortical structure, hippocampus, and amygdala may serve as part of the neuronal network that attaches cognitive significance to fear-

inducing events and facilitates memory traces that enable the individual to rapidly initiate adaptive behavioral responses.

Hypothalamus

The hypothalmic nuclei receive projections from many limbic and brain stem structures (amygdala, septum, piriform cortex, locus coeruleus, dorsal motor nucleus of the vagus), and project to sympathetic regions in the spinal cord and medulla (113). In this context, many of the neuroendocrine and autonomic changes resulting from stress, fear, and anxiety can be understood.

Uncontrollable stress and conditioned fear produces increases in norepinephrine turnover in the hypothalamic nuclei, including the paraventricular nucleus (PVN) (114,115). Further, stimulation of the LC produces increases in NE turnover in the PVN and supraoptic nucleus (SON) (116), indicating an important functional linkage between the LC and the hypothalamus.

The afferent (LC, lateral tegmentum, nucleus of solitary tract cell ventrolateral medulla) and efferent (lower brain stem, intermediolateral cell column of spinal cord, median eminence) projections of the PVN emphasize the PVN's importance in regulation of neuropeptide release and sympathoadrenal outflow associated with anxiety and fear. The PVN is a major contributor to the increased release of CRH, which occurs following stress (117–120). The functional interactions with the LC also apply here, because norepinephrine stimulates CRH release from the PVN. The PVN and SON synthesize the neuropeptides enkephalin, vasopressin, and oxytocin, hormones whose levels are increased by stress (121–124).

The medial basal hypothalamic nuclei (arcuate, ventromedial, periventricular) give rise to fibers that terminate in the median eminance, where a number of hormonal releasing and inhibitory factors are released. There is evidence that stress induces changes in cholecystokinin (CCK) and substance P concentrations in the hypothalamus, suggesting that these peptides may also be involved in a integrated hypothalamic response to anxiety and fear (125).

Orbitofrontal Cortex

The orbitofrontal cortex receives projections from visual, auditory, and somatosensory cortex. It also receives projections from the amygdala, entorhinal cortex, and cingulate gyrus, as well as the mediodorsal thalamic nucleus, which itself receives inputs from the amygdala, septum, and cingulate gyrus (126–129). Efferent pathways from the orbitofrontal region include brain regions that regulate autonomic, neuroendocrine, and skeletal motor function (127,130–132).

An important observation is that a number of sensory responses of orbitofrontal neurons are highly dependent on the meaning of the stimulis. The orbitofrontal cortex may possess information on the reinforcement associations of particular stimuli and may be able to modify this information based upon an individual's recent experience. The orbitofrontal neurons activated after an animal has made responses to specific stimuli may code the characteristics of the experience (rewarding or adverse) and, therefore, be integral to a neural mechanism for rapidly altering the reinforcement associations (133). Thus, the orbitofrontal cortex may be involved in the processing of the effectiveness of the individual's behavior (i.e., the capacity to inhibit and change behavior in the face of changing circumstances such as a threat) (134,135).

Given the reciprocal interactions between subcortical limbic structures and the orbitofrontal region, these two regions may interact in the learning and unlearning of the significance of fear-producing sensory events and in the choice and implementation of behaviors important for survival (136). This hypothesis is consistent with observations that damage to the prefrontal cortex in both experimental animals and humans produces profound changes in mood, affect, and social behavior. Patients with frontal lobe lesions or damage exhibit perservative behavior such that they continue to make the same re-

sponse to a particular situation, even when the response is no longer appropriate (134–137).

NEURAL MECHANISMS THAT CONTRIBUTE TO PERSISTENT SYMPTOMS FOLLOWING TRAUMATIC STRESS (Table 1)

Fear Conditioning

In many patients with PTSD, vivid memories of a traumatic event, autonomic arousal, and even flashbacks can be elicited by diverse sensory and cognitive stimuli that have been associated with the original trauma (138,139). Consequently, patients begin to avoid these stimuli in their everyday life, or a numbing of general emotional responsiveness occurs. Modality-specific and contextual fear conditioning, which are easily demonstrated in the laboratory, may explain some of these observations. Animals exposed to emotionally neutral, visual or auditory conditioned stimuli (CS) in conjunction with an aversive unconditioned stimulus (UCS) will subsequently exhibit a conditioned emotional response (CER) to the CS in the absence of the UCS. The CERs are also produced when an animal is placed in an environment in which an aversive UCS has previously been experienced. In this circumstance the CER is not elicited by a modality-specific stimulis that was paired with a UCS, but instead by complex, polymodal contextual stimuli that were present in the environment when the UCS originally occurred and are present upon reexposure to the environment (106). The CERs can last for years in laboratory animals (140) and are used to infer that a state of fear has been produced (141). Therefore, a neural analysis of fear conditioning in animals may be useful in identifying the neurochemicals and brain structures involved in learning and remembering associations of stimuli with traumatic events, which may form the basis of many of the symptoms associated with PTSD.

TABLE 1. *Neural mechanisms related to the pathophysiology and treatment of PTSD*

Mechanism	Brain structures	Clinical relevance	
		Pathophysiology	Treatment
Fear Conditioning	Sensory Cortex Amygdala Locus Coeruleus Thalamus Hypothalamus	May account for common clinical observation in PTSD that sensory and cognitive stimuli associated with or resembling the original frightening experience elicit panic attacks, flashbacks, and a variety of autonomic symptoms. Pervasive anxiety may be due to contextual fear conditioning.	Psychotherapies designed to reverse the effects of modality-specific fear conditioning are very efficacious. Development of drugs that act selectively on the sensory pathways afferent to the anxiety circuit may decrease conditioned fear.
Extinction	Sensory Cortext Amygdala	A failure in neural mechanisms underlying extinction may relate to treatment-resistant phobias. In PTSD it may relate to persistence in recalling traumatic memories.	Psychotherapies need to be developed that facilitate extinction through use of conditioned inhibitors and learning of "new memories."
Sensitization	Nucleus Accumbens Amygdala Striatum Hypothalamus	May explain adverse effects of early life trauma on subsequent responses to stressful life events. May play a role in the chronic course of PTSD and, in some cases, the worsening of the illness over time.	Suggests efficacy of treatment may vary according to stage of evolution of the disease process. Emphasizes importance of early treatment intervention.

Fear conditioning to sensory modality-specific stimuli (i.e., auditory, visual) can be mediated by subcortical mechanisms involving sensory pathways that project to the thalamus, amygdala, and modality-specific sensory processing areas of the cortex (8). It has been suggested that emotional memories established via thalamoamygdala pathways may be relatively indelible (142). The fear-potentiated acoustic startle paradigm has been particularly useful for delineation of the mechanisms of fear conditioning, because fear is measured by a change in a simple reflex mediated by a defined neural pathway in the brain stem and spinal cord. This test is sensitive to anxiolytic drugs and is disrupted by anatomical lesions known to affect conditioned fear (143). It may be especially informative regarding PTSD given that many PTSD patients exhibit increased startle responses (144), an abnormality generally not reported in other psychiatric disorders. The central nucleus of the amygdala plays a critical role in the fear-potentiated startle response, because it projects directly to one of the brain stem nuclei necessary for startle (145) and lesions of this pathway block the ability of conditioned or unconditioned fear stimuli to elevate startle (146,147). Neurochemical systems involved in regulation of the fear-potentiated startle response include the noradrenergic, dopaminergic, opiate, NMDA, and corticotropin-releasing systems (4).

Contextual fear conditioning involves more complex stimuli from multiple sensory modalities, and projections to the amygdala from higher order cortical areas that integrate inputs from many sources and the hippocampus may be required (106,109). It is noteworthy that lesions of the hippocampus 1 day after fear conditioning abolish contextual fear. Lesions 7 days or longer after fear conditioning have no effect. These finding suggest that the hippocampus may have a time-limited role in associative fear memories evoked by contextual sensory (polymodal), but not unimodal sensory stimuli (109).

Contextual fear conditioning appears to require exposure to a more aversive UCS than modality-specific fear conditioning. Apparently, as the intensity of the UCS increases, the organism becomes more sensitive to a wider range of stimulus factors in the environment. This finding is consistent with clinical data suggesting that the severity of trauma exposure correlates with the severity of PTSD symptomatology.

Extinction

It is possible that the continued ability of conditioned stimuli to elicit a spectrum of anxiety and fear behaviors results from a deficit in the neural mechanisms involved in response reduction or extinction. Experimental extinction is defined as a loss of a previously learned CER following repeated presentations of a conditioned fear stimulus in the absence of a contiguous traumatic event. Extinction has been explained in terms of either an erasure of the original associations that led to the production of the conditioned response (148) or the acquisition of new associations that compete with or mask the expression of the still intact, response-producing associations (149). The erasure hypothesis predicts that, following nonreinforcement, the response-producing associations no longer exist and, therefore, the conditioned response can no longer be performed. The masking hypothesis predicts that the response-producing associations remain after nonreinforcement and, therefore, if it were possible to temporarily remove the masking associations, the conditioned response could be performed.

Several lines of evidence suggest that the original associations are intact following extinction. Expression of extinction may be specific to the stimulus context in which nonreinforcement occurred (150–152). Representation of the unconditioned stimulus even up to 1 year after extinction is sufficient for reinstating extinguished responding to a preextinction level (153–156). These data indicate the essentially permanent nature of conditioned fear and the apparent fragility of extinction. This phenomenon may help to explain the common clinical observation that traumatic memories may remain dormant for many years, only to be elicited by a subsequent stressor or unexpectedly by a stimulus long ago associated with the original trauma (157,158).

These studies indicate that extinction does not erase the original aversive memory, but instead involves the learning of a new memory that masks or inhibits the original one. It is important to emphasize, however, that although extinction can be overcome, in normal animals extinction does result in a reduction of the conditioned fear response. Using traditional measures of conditioned fear such as freezing, potentiated startle, or autonomic indices, nonreinforcement leads to a reduction in all these measures. In healthy humans, many childhood fears become extinguished and do not intrude daily in adulthood. In contrast, PTSD patients describe persistent traumatic memories that do not extinguish. Thus, it is conceivable that some anxiety disorder patients have deficits in brain systems involved in extinction.

The amygdala is not only involved in the acquisition and expression of conditioned fear responses, but may also be necessary for extinction. The NMDA antagonists infused into the amygdala prevent the extinction of fear-potentiated startle (159). Thus, activity in the amygdala during nonreinforced stimuli presentations may be essential for extinction of conditioned fear stimuli. This may result from processes within the amygdala itself, or via structures that project to the amygdala (e.g., hippocampus, prefrontal cortex, septal area) and have been implicated in extinction in several experimental paradigms. Extinction of conditioned fear responses may represent an active suppression by the cortex of subcortical neural circuits (thalamus, amygdala) that maintain learned associations over long time periods (160).

Behavioral Sensitization

Sensitization generally refers to the increase in behavioral or physiological responsiveness that occurs following repeated exposure to a stimulus. Behavioral sensitization can be generally context dependent or conditioned, such that animals will not demonstrate sensitization if the stimulus is presented in a different environment (161). However, if the intensity of the stimulis or drug dose is high enough, behavioral sensitization will occur even if the environment is changed. It has been suggested that different mechanisms are called into play with environment-independent sensitization (162).

The neurochemical and neuroanatomical systems mediating environment-dependent and environment-independent behavioral sensitization have begun to be investigated. The mechanisms of the development and maintenance of stress-induced sensitization in mammals have been most extensively studied in catecholaminergic systems.

Single or repeated exposure to a stressor potentiates the capacity of a subsequent stressor to increase dopamine function in the forebrain (163,164) without apparently altering basal dopamine turnover (165–167). Recently, it has been shown that the conditioned components of sensitization are related to increased dopamine release in the nucleus accumbens (168). Behavioral sensitization to stress may also involve alterations in noradrenergic function. Animals previously exposed to a stressor exhibit increased norepinephrine release in the hippocampus (169), hypothalamus (169), and prefrontal cortex (170) upon stressor reexposure.

Dopamine D_2 receptor antagonists block the development but not the maintenance of sensitization. Conversely, alpha$_2$ receptor agonists and benzodiazepine agonists block the maintenance but not the development of sensitization (162). In addition, lesions of the amygdala or the nucleus accumbens block the development of cocaine-induced behavioral sensitization. In contrast, lesions of the hippocampus and frontal cortex have no effect (Pert A, Weiss SRB, unpublished observations).

There is recent evidence that both the environment-dependent and independent forms of sensitization may be associated with changes in gene expression. Immediate-early genes (such as c-fos) act as transcription factors influencing the expression of intermediate substances or late effector genes that could modulate neurotransmitter or peptide receptors in a long-lasting fashion. Conditioned increases in c-fos have been shown to occur (171,172).

The characteristics of behavioral sensitization suggest that it may be involved in the signs and

symptoms of human anxiety. The PTSD may occur in response to a single precipitating event, or alternatively after repeated traumatic events. Severity of illness is positively correlated with the magnitude of the stressor and history of prior trauma. Finally, the stimuli that evoke intrusive memories, flashbacks, and related symptoms in patients are often difficult to determine, and may bear only a distant association to the initial evoking stimulus.

CONCLUDING COMMENTS

Post-traumatic stress disorder is characterized by intrusive traumatic memories manifested by recurring dreams, flashbacks, and psychological distress following: 1) exposure to events that symbolize or resemble the original trauma; 2) persistent avoidance of stimuli associated with the trauma or a numbing of general responsiveness; and 3) persistent symptoms of increased arousal. The neurobiological basis of some of the symptoms of PTSD can be understood in the context of neural circuits and neural mechanisms of anxiety and fear (173).

Memories and previously learned behaviors influence responses to fear-inducing stimuli via such neural mechanisms as fear conditioning, extinction, and sensitization. Although within the medial temporal lobe memory system, emotional responsiveness (amygdala) and memory (hippocampus) may be separately organized, there is considerable interaction between storage and recall of memory and affect. This is exemplified by the critical role of the amygdala in conditioned fear acquisition, sensitization, extinction, and the attachment of affective significance to neutral stimuli.

The hippocampus and amygdala are sites of convergent reciprocal projections from widespread unimodal and polymodal cortical association areas. It is probably through these interactions, as well as cortical-cortical connections, that memories stored in the cortex, which are continually being reinforced by ongoing experience, are intensified and develop greater coherence (108).

The hippocampal memory system is essential to short-term memory. However, long-term memory storage may be organized such that, as time passes, with subsequent additional retrieval opportunities and the acquisition of related material, the role of the hippocampus diminishes until it may no longer be necessary for memory. The repository of long-term memory may be in the same areas of cortex where the initial sensory impressions take place (174). The shift in memory storage to the cortex may represent a shift from conscious representational memory to unconscious memory processes that indirectly affect behavior.

Therefore, once a fear- or anxiety-inducing sensory stimulis is relayed through the thalamus into neural circuits involving the cortex, hippocampus, and the amygdala, relevant memory traces of past traumatic experiences are stimulated. It is likely that the potency of the cognitive and somatic responses to the stimulis will be strongly correlated with prior experiences due to the strengthening of neural connections within the circuit. These functional neuroanatomical relationships can explain how a single sensory stimulus such as a sight or sound can elicit a specific memory. Moreover, if the sight or sound was associated with a particular traumatic event, a cascade of anxiety- and fear-related symptoms will ensue.

The persistence of intrusive memories may be due to the strength of neuronal interactions between cortical regions where many such memories are stored and subcortical regions, such as the amygdala, which serve to attach affect to the memories. The psychological distress and physiological responses to trauma reminders involve the mechanisms of fear conditioning and extinction. Contextual fear conditioning may be particularly relevant to severe cases of PTSD for whom stimulis generalization is a cardinal feature. The autonomic hyperarousal may be symptoms mediated by brain structures of the efferent arm of the anxiety circuit.

The PTSD is a chronic illness. It has been suggested that the pathophysiology of PTSD should be viewed as a continuously evolving neural process. The disorder is characterized by recurrent panic attacks, flashbacks, conditioned

phobic behavior, and illness exacerbation by stressful life events. Through the process of sensitization, these experiences may lead to formation of neural substrates and new vulnerability factors, resulting in autonomous anxiety symptoms that were previously elicited only by environmental triggers (see Chapter 12 and [175]).

The neural circuit and neural mechanisms of anxiety and fear described in this chapter may have implications for the psychotherapy and pharmacotherapy of PTSD. As noted, fear conditioning may contribute to the symptoms of PTSD. Cognitive-behavior therapies have been designed to reverse the impact of fear conditioning. Panic control treatment, which focuses on reversing the effects of fear conditioning on somatic symptoms associated with the efferent arm of the circuit, has been shown to be particularly effective (176,177). Brain imaging studies can now be conducted before and after the therapy to determine which brain regions are involved in its therapeutic effects. Some patients may not respond to such therapies because of an inability to extinguish intrusive memories and maladaptive behaviors. For such patients, therapies need to be developed that are specifically designed to facilitate extinction through the use of conditioned inhibitors and the learning of "new memories."

The concepts discussed in this chapter also suggest potentially fruitful approaches toward development of new therapeutic drugs for PTSD. Given the central role of the amygdala in the neural mechanisms of fear conditioning, extinction, and sensitization, drugs that act on receptors located on amygdaloid neurons and reduce amygdala activity may be effective in reducing the symptoms associated with these mechanisms. Drugs that act selectively on the sensory pathways afferent to the anxiety-fear circuitry (by presynaptically decreasing the release of neurotransmitters or neuropeptides connecting cortical or subcortical afferents) could be effective in blocking conditioned fear. Alternatively, drugs that selectively decrease the function of brain regions in the efferent arm of the circuit may be effective in reducing the signs and symptoms of anxiety.

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